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Remarks/Arguments

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter. Claims 39-46 and 49-51 are pending in this application and are rejected on various grounds. The rejections to the remaining claims are respectfully traversed.

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

Claims 39-46 and 49-51 are rejected under 35 U.S.C. §101 and 35 USC § 112, first paragraph for lack of utility. The Examiner asserts that he "cannot determine the *degree* to which PRO302 had any effect on vascular permeabilization....making it difficult to determine just how effective PRO302 is at inducing permeability". The Examiner adds that "the mere fact that PRO302 may have an effect on vascular permeabilization is not sufficient grounds for one of skill in the art to assume that it can be used in wound healing and/or diagnosis of a particular disease or condition" and that "the skilled artisan would conclude that the invention lacks specific or substantial utility". Applicants respectfully traverse the rejection.

Applicants present supportive evidence (Exhibit A and B) to show "how effective PRO302 is at inducing permeability." When representative polypeptides like PRO302 (referred to here as BKN or Bolekine) are injected intra-dermally into a guinea pig concurrent with the injection of the Evan's blue dye intra-cardially (Exhibit A), patches of leaked Evans blue dye appear at the site of injection of PRO302 due to vascular leak. The results of a representative experiment is shown in Exhibit B: showing results with saline control, 1 μg VEGF (positive control), test samples -2 different lots of a representative test polypeptide and 10 μg IL-8 (negative control). As evidenced by these results, it is very easy to monitor the ability of polypeptides like PRO302 to induce vascular leakage compared to a negative and a positive control.

Further addressing utility, Applicants submit that based on the results of the vascular leak assay, one skilled in the art would know to use anti-PRO302 antagonists (antibodies) to stop vascular leakage, for example, in pulmonary leakage, capillary leakage, tumor leakage, or in burns. Applicants submit that PRO302's utility lies in its use as a target for the development of anti-vascular leakage agents (as in the case of anti-VEGF antibodies). Such uses are substantial, credible and specific and would be clearly evident to a person skilled in the art. In explaining the "substantial utility" standard, the M.P.E.P. 2107.01 cautions that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used

in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified** for the invention that can be viewed as providing a public benefit **should be accepted as sufficient**, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . **and the assertion would be considered credible by a person of ordinary skill in the art,** do not impose a rejection based on lack of utility (emphasis added)."

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections - 35 USC § 112, first paragraph- enablement

Claims 39-44, 47-48, 50-51 were rejected under 35 U.S.C. §112, first paragraph for lack of enablement.

Applicants respectfully remind the Examiner that the level of skill, knowledge and the level of predictability in the art need to be considered before determining whether the amount of experimentation is undue. In *In re Wands*, the courts concluded that the amount of experimentation needed was not undue in view of the direction and guidance provided by the Appellants and the level of skill in the art (see below).

> "the court held that ....there was 'considerable direction and guidance' in the specification; there was 'a high level of skill in the art at the time the application was filed;' and all the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406; M.P.E.P. 2164.01(a)

As discussed above, from the data disclosed in the specification, specifically on the vascular permebablity assay, the skilled artisan would know that PRO302 can be used as a target to develop therapeutic molecules that stop vascular leakage. While it is true that the skilled artisan may need to conduct experiments to determine the uses of anti- PRO302 *in vivo* to stop vascular

leakage, as in the *Wands* case, such experimentation is not undue. The level of skill in the pertinent field at the time of filing was very sophisticated, as evidenced by the fact that those skilled in the art generally possessed either an M.D. or a Ph. D or both degrees in addition to vast experience. Instead, given the Applicants' guidance in the present disclosure together with the existing knowledge in the art, the skilled artisan would have found it routine to evaluate how to stop vascular leaks *in vivo* with anti-PRO302.

Accordingly, based on the identification of PRO302 as a molecule that increases vascular permeability and the utility of anti-PRO302 stopping vascular leaks, those skilled in the art would readily know how to make and use the present invention.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejections under 35 U.S.C. §112, first paragraph for lack of enablement.

Claim Rejections - 35 USC § 112- written description

Claims 39-44, 47-48, 50-51 were rejected under 35 U.S.C. §112, first paragraph for lack of showing of possession of the claimed invention.

The Examiner alleges that the claims encompass a large number of sequence variants of the protein described by SEQ ID NO: 255 that must retain the ability to enhance vascular permeability in an organism but that there was no discussion in the prior art of instant specification concerning domains or specific amino acid residues responsible for vascular permeabilization activity. Applicants respectfully traverse this rejection.

Initially, Applicants submit that claim 44 is inappropriately rejected under this category since Applicants have clearly shown possession of the polypeptides recited in this claim as of the effective filing date. Further, Applicants submit that whether a specification shows that Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including level of knowledge and skill in the art, and teaching provided by the specification. The inventor is not required to describe every single detail of his or her invention; an Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA technology. It is well established that the level of skill in this field is relatively high, and is represented by a Ph.D. scientist having several years of experience in the pertinent field. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The present invention concerns isolated polypeptides having 80%, 85%, 90%, or 99% sequence identity with a disclosed polypeptide sequence with a functional limitation wherein the claimed polypeptides are "capable of enhancing vascular permeability". The specification further provides detailed description about the cloning and expression of variants of the polypeptides like PRO302 (see, *e.g.*, pages 112-117). The specification further disclosed that screening methods for secretory proteins, which include proteases, were known in the art at the time of filing: "Examples of screening methods and techniques are described in the literature (see, Klein et al....; Proc. Natl. Acad. Sci., 93: 7108-7113 (1996)), page 29, line 33. Thus, the specification provides sufficient information about structural characteristics of the variants in the claimed genus and further demonstrates how variants could be obtained. Case law and the Written description training materials clearly acknowledge that the written description requirements can be met by a combination of structural and functional characteristics shared by members of the genus, as is done in the present case. Thus, the skilled artisan would reasonably conclude that Applicants had possession of the claimed polypeptides at the effective filing date.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C39).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: March 2, 2004

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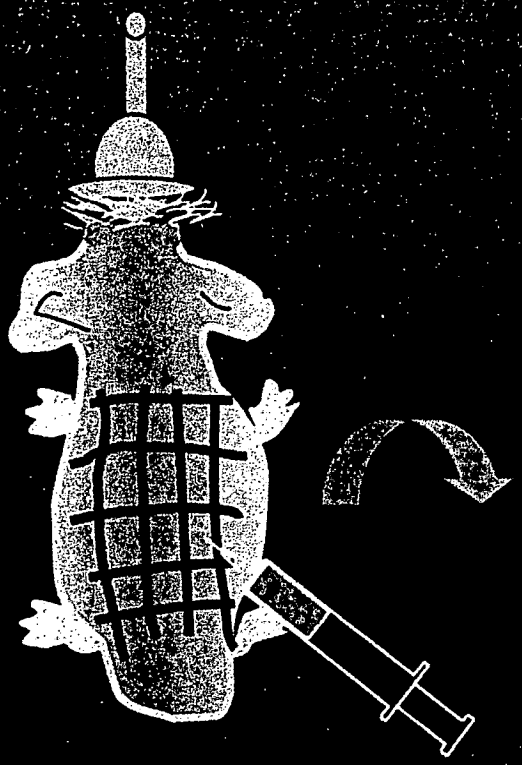
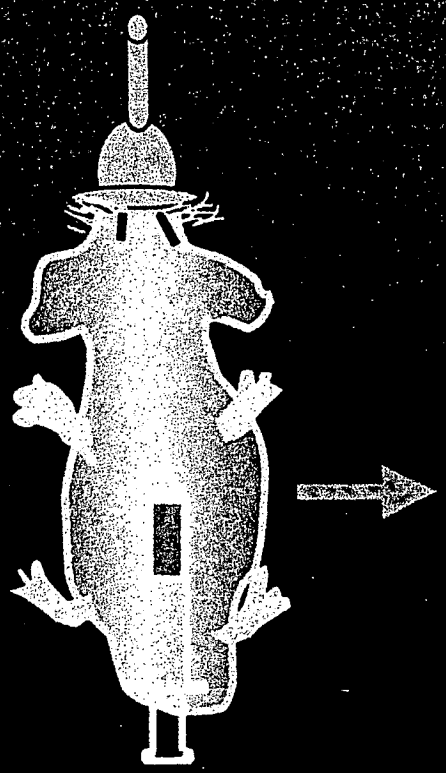
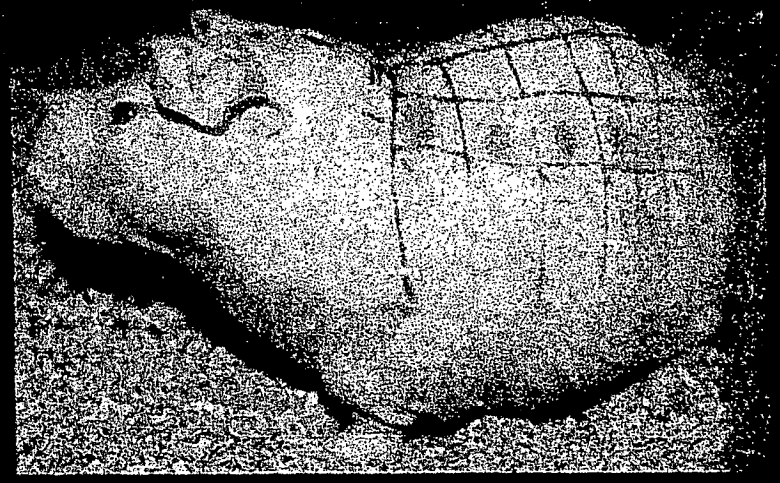
In Vivo Assay for Vascular Leak



Intra-dermal
BKN



Intra-cardiac
Evan's blue



"Horatio"

Bolekine Induces Vascular Leak

Saline

1 μg VEGF

10 μg BKN lot 1

10 μg BKN lot 2

10 μg IL-8